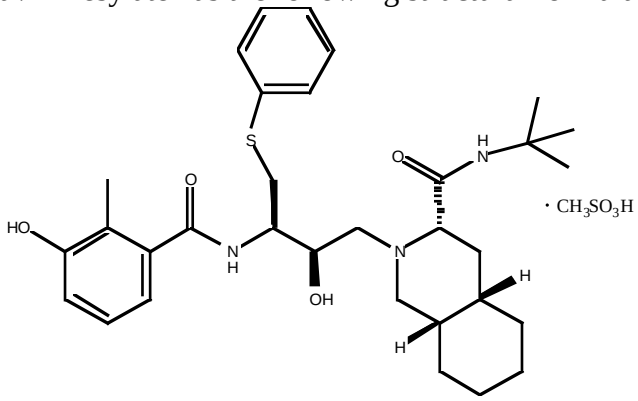
AGOURON PHARMACEUTICALS, INC.
La Jolla, CA 92037, USA

VIRACEPT®

(nelfinavir mesylate)
TABLETS and ORAL POWDER

DESCRIPTION

VIRACEPT® (nelfinavir mesylate) is an inhibitor of the human immunodeficiency virus (HIV) protease. VIRACEPT Tablets are available for oral administration as a light blue, capsule-shaped tablet with a clear film coating in a 250 mg strength (as nelfinavir free base). Each tablet also contains the following inactive ingredients: calcium silicate, crospovidone, magnesium stearate, FD&C blue #2 powder, hydroxypropyl methylcellulose and triacetin. VIRACEPT Oral Powder is available for oral administration in a 50 mg/g strength (as nelfinavir free base) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame, sucrose palmitate, and natural and artificial flavor. The chemical name for nelfinavir mesylate is [3*S*-[2(2*S**, 3*S**), 3α,4aβ,8aβ]]-*N*-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinolinecarboxamide mono-methanesulfonate (salt) and the molecular weight is 663.90 (567.79 as the free base). Nelfinavir mesylate has the following structural formula:



Nelfinavir mesylate is a white to off-white amorphous powder, slightly soluble in water at pH $\leq$4 and freely soluble in methanol, ethanol, isopropanol and propylene glycol.

MICROBIOLOGY

Mechanism of Action: Nelfinavir is an inhibitor of the HIV-1 protease. Inhibition of the viral protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus.

Antiviral Activity In Vitro: The antiviral activity of nelfinavir *in vitro* has been demonstrated in both acute and/or chronic HIV infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against several laboratory strains of HIV-1 and several clinical isolates of HIV-1 and the HIV-2 strain ROD. The EC_{95} (95% effective concentration) of nelfinavir ranged from 7 to 196 nM. In combination with reverse transcriptase inhibitors, nelfinavir demonstrated additive (didanosine or stavudine) to synergistic (zidovudine, lamivudine or zalcitabine) antiviral activity *in vitro* without enhanced cytotoxicity. Drug combination studies with protease inhibitors (ritonavir, saquinavir or indinavir) showed variable results ranging from antagonistic to synergistic.

Drug Resistance: HIV-1 isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=195, 157 of which were evaluable) changes in clinical trials over a period of 2 to 82 weeks**.** One or more virus protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in >10% of patients with evaluable isolates. Of 19 patients for which both phenotypic and genotypic analyses were performed on clinical isolates, 9 showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. All 9 patients possessed one or more mutations in the virus protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

The overall incidence of the D30N mutation in the virus protease of evaluable patients (n=157) receiving nelfinavir monotherapy or nelfinavir in combination with zidovudine and lamivudine or stavudine was 54.8%. The overall incidence of other mutations associated with primary protease inhibitor resistance was 9.6% for the L90M substitution whereas substitutions at 48, 82, or 84 were not observed.

Cross-resistance: *Preclinical Studies*- HIV isolates obtained from 5 patients during nelfinavir therapy showed a 5- to 93-fold decrease in nelfinavir susceptibility *in vitro* when compared to matched baseline isolates, but did not demonstrate a concordant decrease in susceptibility to indinavir, ritonavir, saquinavir or amprenavir, *in vitro*. Conversely, following ritonavir therapy 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) in vitro compared to baseline also exhibited decreased susceptibility to nelfinavir in vitro (5- to 40-fold). An HIV isolate obtained from a patient receiving saquinavir therapy showed decreased susceptibility to saquinavir (7-fold), but did not demonstrate a concordant decrease in susceptibility to nelfinavir. Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. Clinical isolates (n=5) with decreased susceptibility to zidovudine, lamivudine, or nevirapine remain fully susceptible to nelfinavir in vitro.

Clinical Studies- There have been no controlled or comparative studies evaluating the virologic response to subsequent protease inhibitor-containing regimens in patients who have demonstrated loss of virologic response to a nelfinavir-containing regimen. However, virologic response was evaluated in a single-arm prospective study of 26 patients with extensive prior antiretroviral experience with reverse transcriptase inhibitors (mean 2.9) who had received VIRACEPT for a mean duration of 59.7 weeks and were switched to a ritonavir (400 mg BID)/saquinavir hard-gel (400 mg BID) containing regimen after a prolonged period of VIRACEPT failure (median 48 weeks). Sequence analysis of HIV-1 isolates prior to switch demonstrated a D30N or an L90M substitution in 18 and 6 patients, respectively. Subjects remained on therapy for a mean of 48 weeks (range 40 to 56 weeks) where 17 of 26 (65%) subjects and 13 of 26 (50%) subjects were treatment responders with HIV RNA below the assay limit of detection (Chiron bDNA) at 24 and 48 weeks, respectively.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic properties of nelfinavir were evaluated in healthy volunteers and HIV-infected patients; no substantial differences were observed between the two groups.

Absorption: In a pharmacokinetic study in HIV-positive patients, multiple dosing with 750 mg (three 250 mg tablets) three times daily (TID) for 28 days (11 patients) achieved peak plasma concentrations (C_{max}) of 3.0 +/- 1.6 mg/L and morning and afternoon trough concentrations of 1.4 +/- 0.6 mg/L and 1.0 +/- 0.5 mg/L, respectively. In the same study, multiple dosing with 1250 mg (five 250 mg tablets) twice daily (BID) for 28 days (10 patients) achieved C_{max} of 4.0 +/- 0.8 mg/L and morning and evening trough concentrations of 2.2 +/- 1.3 mg/L and 0.7 +/- 0.4 mg/L, respectively. The difference between morning and

afternoon or evening trough concentrations for the TID and BID regimens was also observed in healthy volunteers who were dosed at precise 8- or 12-hour intervals.

Effect of Food on Oral Absorption: Maximum plasma concentrations and area under the plasma concentration-time curve (AUC) were 2 to 3-fold higher under fed conditions compared to fasting. The effect of food on nelfinavir absorption was evaluated in two studies (n=14, total). The meals evaluated contained 517 to 759 Kcal, with 153 to 313 Kcal derived from fat.

Distribution: The apparent volume of distribution following oral administration of nelfinavir was 2-7 L/kg. Nelfinavir in serum is extensively protein-bound (>98%).

Metabolism: Unchanged nelfinavir comprised 82-86% of the total plasma radioactivity after a single oral 750 mg dose of ^{14}C-nelfinavir. *In vitro*, multiple cytochrome P-450 isoforms including CYP3A are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found in plasma. The major oxidative metabolite has *in vitro* antiviral activity comparable to the parent drug.

Elimination: The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87%) of an oral 750 mg dose containing ^{14}C-nelfinavir was recovered in the feces; fecal radioactivity consisted of numerous oxidative metabolites (78%) and unchanged nelfinavir (22%). Only 1-2% of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

Special Populations

Hepatic or Renal Insufficiency: The pharmacokinetics of nelfinavir have not been studied in patients with hepatic or renal insufficiency; however, less than 2% of nelfinavir is excreted in the urine, so the impact of renal impairment on nelfinavir elimination should be minimal.

Gender and Race: No significant pharmacokinetic differences have been detected between males and females. Pharmacokinetic differences due to race have not been evaluated.

Pediatrics: see PRECAUTIONS: Pediatric Use

Geriatric Patients: The pharmacokinetics of nelfinavir have not been studied in patients over 65 years of age.

Drug Interactions (also see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions)

The potential ability of nelfinavir to inhibit the major human cytochrome P450 isoforms (CYP3A, CYP2C19, CYP2D6, CYP2C9, CYP1A2 and CYP2E1) has been investigated *in vitro*. Only CYP3A was inhibited at concentrations in the therapeutic range.

Specific drug interaction studies were performed with nelfinavir and a number of drugs. Tables 1 summarizes the effects of nelfinavir on the geometric mean AUC and C_{max} of coadministered drugs. Table 2 shows the effects of coadministered drugs on the geometric mean AUC and C_{max} of nelfinavir.

Table 1: Drug Interactions
Effect of Nelfinavir on Coadministered Drug Plasma AUC and C_{max}

Coadministered Drug	Nelfinavir Dose	N	Coadministered Drug	
			AUC (95%CI)	C_{max} (95%CI)
Lamivudine 150 mg Single Dose	750 mg q8h x 7-10 days	11	↑10% (1-20%)	↑31% (5-62%)
Stavudine 30-40 mg bid x 56 days	750 mg tid x 56 days	8	↔	↔
Zidovudine 200 mg Single Dose	750 mg q8h x 7-10 days	11	↓35% (28-41%)	↓31% (8-49%)
Indinavir 800 mg Single Dose	750 mg q8h x 7 days	6	↑51% (25-83%)	↔
Ritonavir 500 mg Single Dose	750 mg q8h x 5 doses	10	↔	↔
Saquinavir 1200 mg Single Dose[1]	750 mg tid x 4 days	14	↑392% (271-553%)	↑179% (105-280%)
Efavirenz: 600 mg qd x 7 days	750 mg q8h x 7 days	10	↔	↔
Ethinyl estradiol 35 µg qd x 15 days	750 mg q8h x 7 days	12	↓47% (41-63%)	↓28% (14-39%)
Norethindrone 0.4 mg qd x 15 days	750 mg q8h x 7 days	12	↓18% (12-27%)	↔
Rifabutin 150 mg qd x 8 days [2]	750 mg q8h x 7-8 days [3]	12	↑83% (69-99%)	↑19% (9-30%)
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	↑207% (151-276%)	↑146% (112-186%)

Table 2: Drug Interactions
Effect of Coadministered Drug on Nelfinavir Plasma AUC and C_{max}

Coadministered Drug	Nelfinavir Dose	N	Nelfinavir	
			AUC (95%CI)	C_{max} (95%CI)
Didanosine 200 mg Single Dose	750 mg Single Dose	9	↔	↔
Zidovudine 200 mg + Lamivudine 150 mg Single Dose	750 mg q8h x 7-10 days	11	↔	↔
Indinavir 800 mg q8h x 7 days	750 mg Single Dose	6	↑83% (34-150%)	↑31% (13-52%)
Ritonavir 500 mg q12h x 3 doses	750 mg Single Dose	10	↑152% (86-242%)	↑44% (25-67%)
Saquinavir 1200 mg tid x 4 days[1]	750 mg Single Dose	14	↑18% (5-33%)	↔
Efavirenz 600 mg qd x 7 days	750 mg q8h x 7 days	10	↑20% (5-38%)	↑21% (8-36%)
Ketoconazole 400 mg qd x 7 days	500 mg q8h x 5-6 days	12	↑35% (21-49%)	↑25% (8-44%)
Nevirapine 200 mg qd x 14 days Followed by 200 mg bid x 14 days	750 mg tid x 36 days	23	↔	↔
Rifabutin 150 mg qd x 8 days	750 mg q8h x 7-8 days	11	↓23% (12-33%)	↓18% (6-29%)
	1250 mg q12h x 7-8 days	11	↔	↔
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	↓32% (10-48%)	↓25% (6-38%)
Rifampin 600 mg qd x 7 days	750 mg q8h x 5-6 days	12	↓82% (77-86%)	↓76% (67-83%)

↑ Indicates increase

↓ Indicates decrease

↔ Indicates no change (p value > 0.05)

[1] Using the soft gelatin capsule formulation of saquinavir 1200mg

[2] Rifabutin 150mg qd changes in Table 1 are relative to Rifabutin 300mg qd x 8 days without coadministration with nelfinavir

[3] Comparable changes in rifabutin concentrations were observed with VIRACEPT 1250mg q12h x 7 days

For information regarding clinical recommendations, see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions.

INDICATIONS AND USAGE

VIRACEPT in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Description of Studies

In the clinical studies described below, efficacy was evaluated by the percent of patients with plasma HIV RNA < 400 copies/mL (Studies 511 and 542) or < 500 copies/mL (Study ACTG 364), using the Roche RT-PCR (Amplicor) HIV-1 Monitor or < 50 copies/mL, using the Roche HIV-1 Ultrasensitive assay (Study

Avanti 3). In the analysis presented in each figure, patients who terminated the study early for any reason, switched therapy due to inadequate efficacy or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 400 copies/mL, above 500 copies/mL, or above 50 copies/mL at subsequent time points, depending on the assay that was used.

a. Studies in Antiretroviral Treatment Naïve Patients

Study 511: VIRACEPT + zidovudine + lamivudine versus zidovudine + lamivudine

Study 511 was a double-blind, randomized, placebo controlled trial comparing treatment with zidovudine (ZDV; 200mg TID) and lamivudine (3TC; 150mg BID) plus 2 doses of VIRACEPT (750mg and 500mg TID) to zidovudine (200mg TID) and lamivudine (150mg BID) alone in 297 antiretroviral naive HIV-1 infected patients (median age 35 years [range 21 to 63], 89% male and 78% Caucasian). Mean baseline CD_4 cell count was 288 cells/mm^3 and mean baseline plasma HIV RNA was 5.21 $\log_{10}$ copies/mL (160,394 copies/mL). The percent of patients with plasma HIV RNA < 400 copies/mL and mean changes in CD_4 cell count are summarized in Figures 1 and 2, respectively.

Figure 1

Study 511: Percentage of Patients With HIV RNA Below 400 Copies/mL

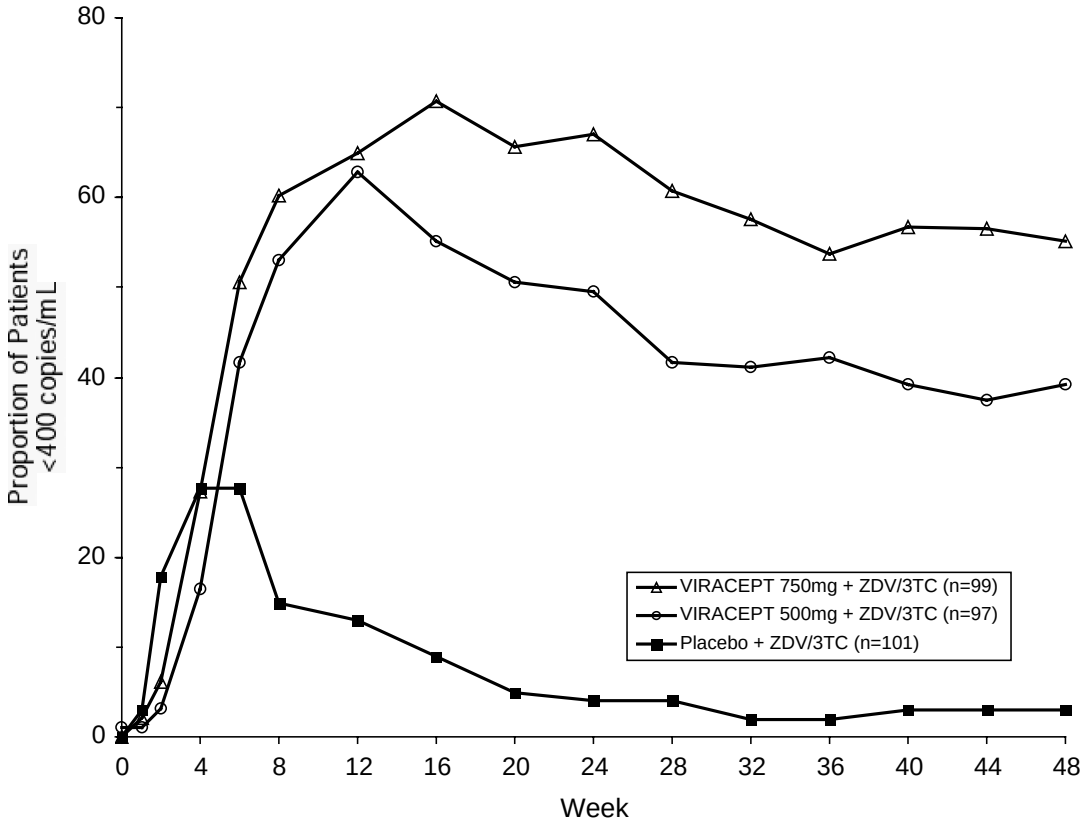
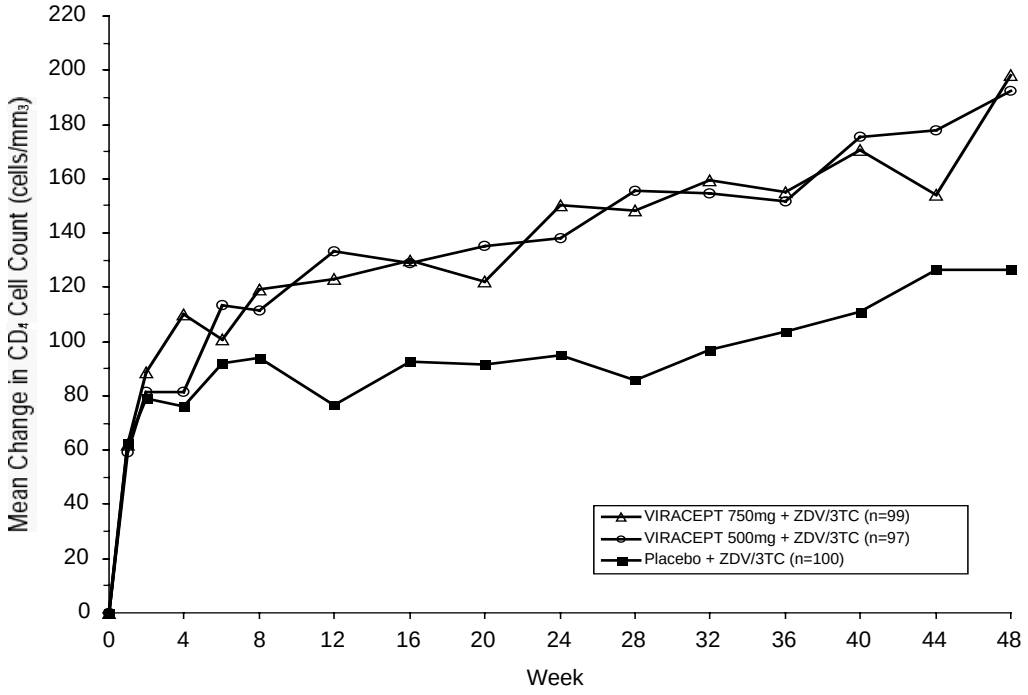


Figure 2

Study 511: Mean Change From Baseline in CD4 Cell Counts



Study 542: VIRACEPT BID + stavudine + lamivudine compared to VIRACEPT TID + stavudine + lamivudine

Study 542 is an ongoing, randomized, open-label trial comparing the HIV RNA suppression achieved by VIRACEPT 1250 mg BID versus VIRACEPT 750 mg TID in patients also receiving stavudine (d4T; 30-40mg BID) and lamivudine (3TC; 150mg BID). Patients had a median age of 36 years (range 18 to 83), were 84% male, and were 91% Caucasian. Patients had received less than 6 months of therapy with nucleoside transcriptase inhibitors and were naïve to protease inhibitors. Mean baseline CD4 cell count was 296 cells/mm^3 and mean baseline plasma HIV RNA was 5.0 $\log_{10}$ copies/mL (100,706 copies/mL).

Results showed that there was no significant difference in mean CD4 count among treatment groups; the mean increases from baseline for the BID and TID arms were 150 cells/mm^3 at 24 weeks and approximately 200 cells/mm^3 at 48 weeks.

The percent of patients with HIV RNA <400 copies/mL is summarized in Figure 3. The outcomes of patients through 48 weeks of treatment are summarized in Table 3.

Figure 3

Study 542: Percentage of Patients With HIV RNA Below 400 Copies/mL

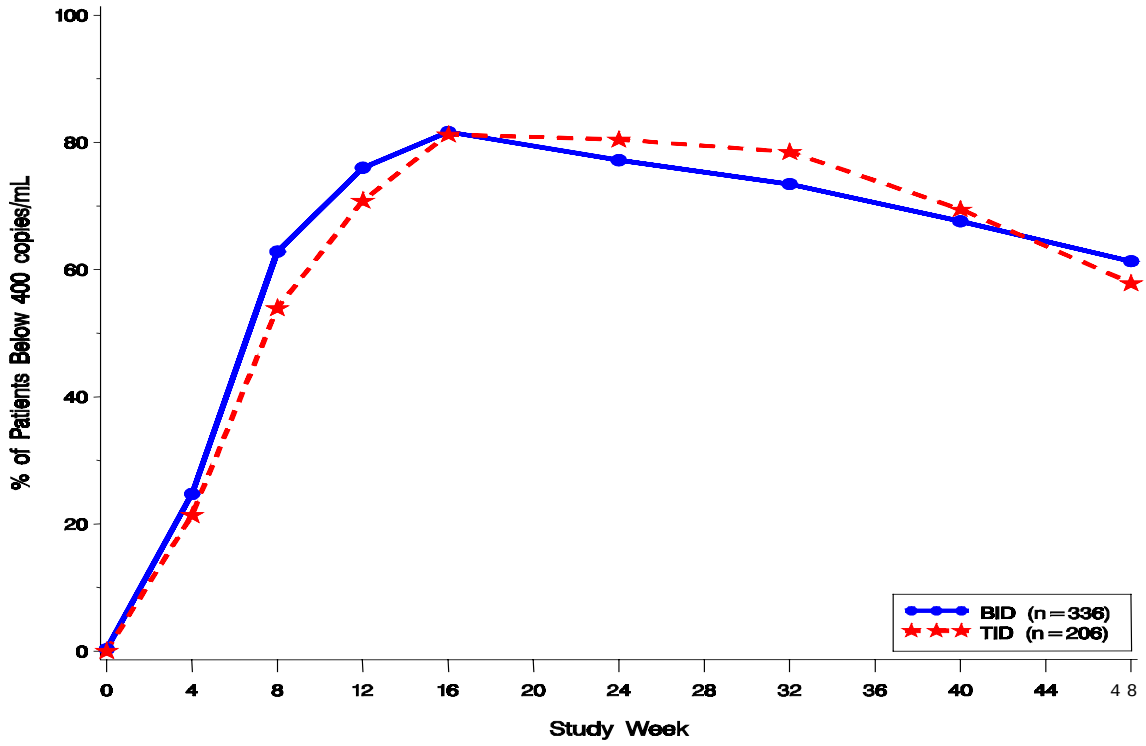


Table 3

Outcomes of Randomized Treatment Through 48 Weeks

Outcome	Viracept 1250 mg BID Regimen	Viracept 750 mg TID Regimen
Number of patients evaluable*	323	192
HIV RNA < 400 copies/ml	198 (61%)	111 (58%)
HIV RNA ≥ 400 copies/ml	46 (14%)	22 (11%)
Discontinued due to VIRACEPT toxicity**	9 (3%)	2 (1%)

Discontinued due to other antiretroviral agents' Toxicity**	3 (1%)	3 (2%)
Others***	67 (21%)	54 (28%)

*Twelve patients in the BID arm and fourteen patients in the TID arm have not yet reached 48 weeks of therapy

**These rates only reflect dose-limiting toxicities that were counted as the initial reason for treatment failure in the analysis (See ADVERSE REACTIONS for a description of the safety profile of these regimens).

***Consent withdrawn, lost to follow-up, intercurrent illness, noncompliance or missing data; all assumed as failures

Study Avanti 3: VIRACEPT TID + zidovudine + lamivudine compared to zidovudine + lamivudine.

Study Avanti 3 was a placebo-controlled, randomized, double-blind study designed to evaluate the safety and efficacy of VIRACEPT (750 mg TID) in combination with zidovudine (ZDV; 300 mg BID) and lamivudine (3TC; 150 mg BID) versus placebo in combination with ZDV and 3TC administered to antiretroviral-naive patients with HIV infection and a CD4 lymphocyte count between 150 and 500 cells/μL. Patients had a mean age of 35 (range 22-59) were 89% male and 88% Caucasian. Mean baseline CD4 cell count was 304 cells/mm^3 and mean baseline plasma HIV RNA was 4.8 $\log_{10}$ copies/mL (57,887 copies/mL). The percent of patients with plasma HIV RNA <50 copies/mL at 52 weeks was 54% for the VIRACEPT + ZDV + 3TC treatment group and 13% for the ZDV + 3TC treatment group.

b. Studies in Antiretroviral Treatment Experienced Patients

Study ACTG 364: VIRACEPT TID + 2NRTIs compared to efavirenz + 2NRTIs compared to VIRACEPT + efavirenz + 2NRTIs

Study ACTG 364 was a randomized, double-blind study that evaluated the combination of VIRACEPT 750 mg TID and/or efavirenz 600 mg QD with 2 NRTIs (either didanosine [ddI]+ d4T, ddI + 3TC, or d4T + 3TC) in patients with prolonged prior nucleoside exposure who had completed 2 previous ACTG studies. Patients had a mean age of 41 years (range 18 to 75), were 88% male, and were 74% Caucasian. Mean baseline CD4 cell count was 389 cells/mm^3 and mean baseline plasma HIV RNA was 3.9 $\log_{10}$ copies/mL (7,954 copies/mL).

The percent of patients with plasma HIV RNA < 500 copies/mL at 48 weeks was 42% , 62% , and 72% for the VIRACEPT, EFV, and VIRACEPT+EFV treatment groups, respectively. The 4-drug combination of VIRACEPT + EFV + 2 NRTIs was more effective in suppressing plasma HIV RNA in these patients than either 3-drug regimen .

CONTRAINDICATIONS

VIRACEPT is contraindicated in patients with clinically significant hypersensitivity to any of its components.

VIRACEPT should not be administered concurrently with, cisapride, triazolam, midazolam, ergot derivatives, amiodarone or quinidine because VIRACEPT may affect the hepatic metabolism of these drugs and create the potential for serious and/or life-threatening adverse events.

WARNINGS

ALERT: Find out about medicines that should not be taken with VIRACEPT. This statement is included on the product's bottle label.

Drug Interactions (Also see PRECAUTIONS)

Nelfinavir is an inhibitor of the P450 isoform CYP3A. Co-administration of VIRACEPT and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects. Nelfinavir is metabolized in part by CYP3A. Coadministration of VIRACEPT and drugs that induce CYP3A may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of VIRACEPT and drugs that inhibit CYP3A may increase nelfinavir plasma concentrations. (Also see **PRECAUTIONS: Table 4: Drugs That Should Not Be Coadministered With VIRACEPT - Table 5: Established Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies – Table 6: Other Potentially Significant Clinical Drug Interactions With VIRACEPT.**)

Concomitant use of VIRACEPT with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including VIRACEPT, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including VIRACEPT, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving protease inhibitors, including VIRACEPT. Coadministration of a protease inhibitor with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. (See PRECAUTIONS, Drug Interactions and Information for Patients, and the complete prescribing information for sildenafil.)

Concomitant use of St. John's wort (hypericum perforatum) or St. John's wort containing products and VIRACEPT is not recommended. Coadministration of St. John's wort with protease inhibitors, including VIRACEPT, is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of VIRACEPT and lead to loss of virologic response and possible resistance to VIRACEPT or to the class of protease inhibitors.

Patients with Phenylketonuria

Patients with Phenylketonuria: VIRACEPT Oral Powder contains 11.2 mg phenylalanine per gram of powder.

Diabetes mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

General

Nelfinavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with hepatic impairment.

Resistance/Cross Resistance

HIV cross-resistance between protease inhibitors has been observed. (see MICROBIOLOGY)

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Redistribution/accumulation of body fat

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information For Patients

"A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with VIRACEPT**. A Patient Package Insert (PPI) for VIRACEPT is available for patient information".

For optimal absorption, patients should be advised to take VIRACEPT with food (See CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Patients should be informed that VIRACEPT is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections.

Patients should be told that there is currently no data demonstrating that VIRACEPT therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should be advised to take VIRACEPT and other concomitant antiretroviral therapy every day as prescribed. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of VIRACEPT is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should be informed that VIRACEPT Tablets are film-coated and that this film-coating is intended to make the tablets easier to swallow.

The most frequent adverse event associated with VIRACEPT is diarrhea, which can usually be controlled with non-prescription drugs, such as loperamide, which slow gastrointestinal motility.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long term health effects of these conditions are not known at this time.

VIRACEPT may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St.

John's wort.

Patients receiving oral contraceptives should be instructed that alternate or additional contraceptive measures should be used during therapy with VIRACEPT.

Patients receiving sildenafil and nelfinavir should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and prolonged penile erection, and should promptly report any symptoms to their doctor.

Drug Interactions (Also see CONTRAINDICATIONS, WARNINGS, CLINICAL PHARMACOLOGY:Drug Interactions)

Nelfinavir is an inhibitor of CYP3A (cytochrome P450 3A). Coadministration of VIRACEPT and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects, see Tables 4, 5 and 6. Nelfinavir is metabolized in part by CYP3A. Coadministration of VIRACEPT and drugs that induce CYP3A, such as rifampin, may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of VIRACEPT and drugs that inhibit CYP3A may increase nelfinavir plasma concentrations.

Drug interaction studies reveal no clinically significant drug interactions between nelfinavir and didanosine, lamivudine, stavudine, zidovudine, efavirenz, nevirapine, or ketoconazole and no dose adjustments are needed. In the case of didanosine, it is recommended that didanosine be administered on an empty stomach; therefore, nelfinavir should be administered with food one hour after or more than 2 hours before didanosine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between VIRACEPT and dapsone, trimethoprim/sulfamethoxazole, clarithromycin, azithromycin, erythromycin, itraconazole or fluconazole.

Table 4
Drugs That Should Not Be Coadministered With VIRACEPT

Drug Class	Drugs Within Class Not to be Coadministered With VIRACEPT
Antiarrhythmics	amiodarone, quinidine
Antimigraine	ergot derivatives
Antimycobacterial agents	rifampin
Benzodiazepines	midazolam, triazolam
GI motility agents	cisapride
HMG-CoA reductase inhibitors	lovastatin, simvastatin

Table 5
Established Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies (see CLINICAL PHARMACOLOGY, for Magnitude of Interaction, Tables 1 and 2)

Drug Name	Effect on Concentration	Clinical Comment
Rifabutin	↑ rifabutin ↓ nelfinavir (750mg TID) ↔ nelfinavir (1250mg BID)	It is recommended that the dose of rifabutin be reduced to one-half the usual dose when administered with VIRACEPT; 1250mg BID is the preferred dose of VIRACEPT when coadministered with rifabutin.
Indinavir	↑ nelfinavir ↑ indinavir	Appropriate doses for this combination with respect to safety and efficacy have not been established.
Ritonavir	↑ nelfinavir	Appropriate doses for this combination, with respect to safety and efficacy, have not been established
Saquinavir	↑ saquinavir	Appropriate doses for this combination with respect to safety and efficacy have not been established.
Oral Contra-ceptives	↓ ethinyl estradiol	Alternative or additional contraceptive measures should be used when oral contraceptives and VIRACEPT are coadministered.

Table 6 Other Potentially Significant Clinical Drug Interactions With VIRACEPT*	
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	May decrease nelfinavir plasma concentrations**
HMG-CoA reductase inhibitors: atorvastatin, cerivastatin,	Plasma concentrations may be increased by VIRACEPT
Immunosuppressants: Cyclosporine Tacrolimus	Plasma concentrations may be increased by VIRACEPT
Erectile dysfunction agents: Sildenafil	Expected to substantially increase sildenafil concentrations (sildenafil should not exceed a maximum single dose of 25 mg in a 48 hour period when administered in patients receiving protease inhibitors; consult sildenafil prescribing information)

* This table is not all inclusive.

** VIRACEPT may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly

Carcinogenesis and Mutagenesis

Carcinogenicity studies in animals have not yet been completed. Nelfinavir was not, however, mutagenic or clastogenic in a battery of *in vitro* and *in vivo* tests including microbial mutagenesis (Ames), mouse lymphoma, chromosome aberrations in human lymphocytes, and an *in vivo* rat micronucleus assay.

Pregnancy, Fertility and Reproduction - Pregnancy Category B

Comparisons of systemic exposure are based on the steady-state area under the plasma concentration time curve (AUC) observed in humans receiving the recommended therapeutic dose. Nelfinavir produced no effects on either male or female mating and fertility or embryo survival in rat studies at exposures comparable to human therapeutic exposure. There were also no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures comparable to human exposure. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight decrease in maternal body weight was observed; however, even at the highest dose evaluated, systemic exposure in rabbits was significantly lower than human exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIRACEPT should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to

VIRACEPT and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats have demonstrated that nelfinavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIRACEPT**.

Pediatric Use

Nelfinavir was studied in one open-label, uncontrolled trial in 38 pediatric patients ranging in age from 2 to 13 years. In order to achieve plasma concentrations in pediatric patients which approximate those observed in adults, the recommended pediatric dose is 20-30 mg/kg given three times daily with a meal or light snack, not to exceed 750 mg three times a day. (see DOSAGE AND ADMINISTRATION).

A similar adverse event profile was seen during the pediatric clinical trial as in adult patients. The evaluation of the antiviral activity of nelfinavir in pediatric patients is ongoing. The evaluation of the safety, effectiveness and pharmacokinetics of nelfinavir in pediatric patients below the age of 2 years is ongoing.

Geriatric Use

Clinical studies of VIRACEPT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

The safety of VIRACEPT was studied in over 5000 patients who received drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving VIRACEPT was diarrhea, which was generally of mild to moderate intensity.

Drug-related clinical adverse experiences of moderate or severe intensity in $\geq$2% of patients treated with VIRACEPT coadministered with d4T and 3TC (Study 542) for up to 48 weeks or with ZDV plus 3TC (Study 511) for up to 24 weeks are presented in Table 7.

Table 7
Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Patients

	Study 511 24 weeks			Study 542 48 weeks	
Adverse Events	Placebo + ZDV/3TC (n=101)	500 mg TID VIRACEPT + ZDV/3TC (n=97)	750 mg TID VIRACEPT + ZDV/3TC (n=100)	1250mg BID VIRACEPT + d4T/3TC (n=344)	750 mg TID VIRACEPT + d4T/3TC (n=210)
Digestive System					
Diarrhea	3%	14%	20%	20%	15%
Nausea	4%	3%	7%	3%	3%
Flatulence	0	5%	2%	1%	1%
Skin/Appendages					
Rash	1%	1%	3%	2%	1%

[1] Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions

Adverse events occurring in less than 2% of patients receiving VIRACEPT in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.
Body as a Whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain and redistribution/accumulation of body fat (See PRECAUTIONS, Fat Redistribution).
Digestive System: anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.
Hemic/Lymphatic System: anemia, leukopenia and thrombocytopenia.
Metabolic/Nutritional System: increases in alkaline phosphate, amylase, creatine phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, dehydration, and liver function tests abnormal.
Musculoskeletal System: arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.
Nervous System: anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence and suicide ideation.
Respiratory System: dyspnea, pharyngitis, rhinitis, and sinusitis.
Skin/Appendages: dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria.
Special Senses: acute iritis and eye disorder.
Urogenital System: kidney calculus, sexual dysfunction and urine abnormality.

Post-Marketing Experience

The following additional adverse experiences have been reported from postmarketing surveillance as at least possibly related or of unknown relationship to VIRACEPT:
Body as a Whole: Hypersensitivity reactions (including bronchospasm, moderate to severe rash, fever and edema).
Digestive System: jaundice
Metabolic/Nutritional System: bilirubinemia, , metabolic acidosis

Laboratory Abnormalities

The percentage of patients with marked laboratory abnormalities in Studies 542 and 511 are presented in Table 8. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline.

Table 8
Percentage of Patients by Treatment Group With Marked Laboratory Abnormalities [1] in >2% of Patients

	Study 511			**Study 542**	
	Placebo + ZDV/3TC (n=101)	500 mg TID VIRACEPT + ZDV/3TC (n=97)	750 mg TID VIRACEPT + ZDV/3TC (n=100)	1250mg BID VIRACEPT + d4T/3TC (n=344)	750 mg TID VIRACEPT + d4T/3TC (n=210)
Hematology					
Hemoglobin	6%	3%	2%	0	0
Neutrophils	4%	3%	5%	2%	1%
Lymphocytes	1%	6%	1%	1%	0
Chemistry					
ALT (SGPT)	6%	1%	1%	2%	1%
AST (SGOT)	4%	1%	0	2%	1%
Creatine Kinase	7%	2%	2%	NA	NA

[1] Marked laboratory abnormalities are defined as a shift from Grade 0 at baseline to at least Grade 3 or from Grade 1 to Grade 4

OVERDOSAGE

Human experience of acute overdose with VIRACEPT is limited. There is no specific antidote for overdose with VIRACEPT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since nelfinavir is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose is 1250 mg (five 250 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily. VIRACEPT should be taken with a meal or light snack. It is recommended that

VIRACEPT be used in combination with nucleoside analogues. Patients unable to swallow tablets may place whole tablets or crushed tablets in a small amount of water to dissolve before ingestion or they may mix crushed tablets in a small amount of food. Once mixed with food or dissolved in water, the entire contents must be consumed in order to obtain the full dose. If it is not consumed immediately, the mixture must be stored under refrigeration for up to 6 hours.

Pediatric Patients (2-13 years): The recommended oral dose of VIRACEPT for pediatric patients 2 to 13 years of age is 20-30 mg/kg per dose, three times daily with a meal or a light snack. The pharmacokinetics of twice daily dosing of VIRACEPT in pediatric patients has not been established. For children unable to take tablets, VIRACEPT Oral Powder may be administered. The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk or dietary supplements; once mixed, the entire contents must be consumed in order to obtain the full dose. The recommended use period for storage of the product in these media is 6 hours under refrigeration. Acidic food or juice (e.g., orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. VIRACEPT Oral Powder should not be reconstituted with water in its original container. The recommended pediatric dose of VIRACEPT to be administered three times daily is described in Table 9:

Table 9 Pediatric Dose to be Administered Three Times Daily

Body Weight		Number of Level 1 gm	Number of Level	Number of
Kg.	lbs.	Scoops	Teaspoons	Tablets
7 to < 8.5	15.5 to < 18.5	4	1	-----
8.5 to < 10.5	18.5 to < 23	5	1 1/4	-----
10.5 to < 12	23 to < 26.5	6	1 1/2	-----
12 to < 14	26.5 to < 31	7	1 3/4	-----
14 to < 16	31 to < 35	8	2	-----
16 to < 18	35 to < 39.5	9	2 1/4	-----
18 to < 23	39.5 to < 50.5	10	2 1/2	2
≥ 23	≥ 50.5	15	3 3/4	3

HOW SUPPLIED

VIRACEPT (nelfinavir mesylate) Tablets, 250 mg are light blue, capsule-shaped tablets with a clear film coating engraved with “VIRACEPT” on one side and “250 mg” on the other.

Available as:

NDC 63010-010-27, bottle containing 270 tablets
NDC 63010-010-30, bottle containing 300 tablets
VIRACEPT (nelfinavir mesylate) Oral Powder, 50 mg/g is an off-white powder containing 50 mg (as nelfinavir free base) in each level scoopful (1 gram).
Available as:
NDC 63010-011-90, multiple use bottle containing 144 grams of powder with scoop.

VIRACEPT Tablets and Oral Powder should be stored at 15 to 30 °C (59° to 86 °F).

Keep container tightly closed. Dispense in original container

Agouron
VIRACEPT
Patient Prescribing
Information

[logo]

[title]

Information for Patients About VIRACEPT® (VI-ra-cept)
Generic Name: nelfinavir (nel-FIN-na-veer) mesylate

For the Treatment of Human Immunodeficiency Virus (HIV) Infection

Please read this information carefully before taking VIRACEPT. Also, please read this leaflet each time you renew the prescription, just in case anything has changed. This is a summary and not a replacement for a careful discussion with your doctor. You and your doctor should discuss VIRACEPT when you start taking this medication and at regular checkups. You should remain under a doctor's care when taking VIRACEPT and should not change or stop treatment without first talking with your doctor.

ALERT: Find out about medicines that should NOT be taken with VIRACEPT. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH VIRACEPT".

[section heading]
What is VIRACEPT and how does it work?

VIRACEPT is used in combination with other antiretroviral drugs in the treatment of people with human immunodeficiency virus (HIV) infection. Infection with HIV leads to the destruction of CD4 T cells, which are important to the immune system. After a large number of CD4 cells have been destroyed, the infected person develops acquired immune deficiency syndrome (AIDS).

VIRACEPT works by blocking HIV protease (a protein-cutting enzyme), which is required for HIV to multiply. VIRACEPT has been shown to significantly reduce the amount of HIV in the blood. Although VIRACEPT is not a cure for HIV or AIDS, VIRACEPT can help reduce your risk for death and illness associated with HIV. Patients who took VIRACEPT also had significant increases in the number of CD4 cell

count.

VIRACEPT should be taken together with other antiretroviral drugs such as Retrovir® (zidovudine, AZT), Epivir® (lamivudine, 3TC), or Zerit® (stavudine, d4T). Taking VIRACEPT in combination with other antiretroviral drugs reduces the amount of HIV in the body (viral load) and raises CD4 counts.

VIRACEPT may be taken by adults, adolescents, and children 2 years of age or older. Studies in infants younger than 2 years of age are now taking place.

[section heading]
Does VIRACEPT cure HIV or AIDS?

VIRACEPT is not a cure for HIV infection or AIDS. People taking VIRACEPT may still develop opportunistic infections or other conditions associated with HIV infection. Some of these conditions are pneumonia, herpes virus infections, *Mycobacterium avium* complex (MAC) infections, and Kaposi’s sarcoma.

There is no proof that VIRACEPT can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

[section heading]
Who should or should not take VIRACEPT?

Together with your doctor, you need to decide whether VIRACEPT is appropriate for you. In making your decision, the following should be considered:

Allergies: If you have had a serious allergic reaction to VIRACEPT, you must not take VIRACEPT. You should also inform your doctor,

nurse, or pharmacist of any known allergies to substances such as other medicines, foods, preservatives, or dyes.

If you are pregnant: The effects of VIRACEPT on pregnant women or their unborn babies are not known. If you are pregnant or plan to become pregnant, you should tell your doctor before taking VIRACEPT.

If you are breast-feeding: You should discuss with your doctor the best way to feed your baby. You should be aware that if your baby does not already have HIV, there is a chance that it can be transmitted through breast-feeding. **Women should not breast-feed if they have HIV.**

Children: VIRACEPT is available for the treatment of children 2 through 13 years of age with HIV. There is a powder form of VIRACEPT that can be mixed with milk, baby formula, or foods like pudding. Instructions on how to take VIRACEPT powder can be found in a later section that discusses how VIRACEPT Oral Powder should be prepared.

If you have liver disease: VIRACEPT has not been studied in people with liver disease. If you have liver disease, you should tell your doctor before taking VIRACEPT.

Other medical problems: Certain medical problems may affect the use of VIRACEPT. Some people taking protease inhibitors have developed new or more serious diabetes or high blood sugar. Some people with hemophilia have had increased bleeding. It is not known whether the protease inhibitors caused these problems. Be sure to tell your doctor if you have hemophilia types A and B, diabetes mellitus, or an increase in thirst and/or frequent urination.

Changes in body fat have been seen in some patients taking protease inhibitors. These changes may include increased amount of fat in the

upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the face, legs and arms may also happen. The cause and long-term health effects of these conditions are not known at this time.

[section heading]
Can VIRACEPT be taken with other medications?

VIRACEPT may interact with other drugs, including those you take without a prescription. You must discuss with your doctor any drugs that you are taking or are planning to take before you take VIRACEPT.

[subhead]

Medicines you should <u>not</u> take with VIRACEPT:

Propulsid® (cisapride, for heartburn)
Cordarone® (amiodarone, for irregular heartbeat)
Quinidine® (for irregular heartbeat), also known as Quinaglute®, Cardioquin®, Quinidex®, and others
Ergot derivatives (Cafergot® and others, for migraine headache)
Halcion® (triazolam)
Versed® (midazolam)
Mevacor® (lovastatin, for cholesterol lowering)
Zocor® (simvastatin, for cholesterol lowering)

Taking the above drugs with VIRACEPT may cause serious and/or life-threatening adverse events.

Rifampin® (for tuberculosis), also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®
This drug reduces blood levels of VIRACEPT.

[subhead]
Dose reduction required if you take VIRACEPT with: Mycobutin® (rifabutin, for MAC); you will need to take a lower dose of Mycobutin.

[subhead]
A change of therapy should be considered if you are taking VIRACEPT with:
Phenobarbital
Phenytoin (Dilantin® and others)
Carbamazepine (Tegretol® and others)
These agents may reduce the amount of VIRACEPT in your blood and make it less effective.

Oral contraceptives (“the pill”)
If you are taking the pill to prevent pregnancy, you should use a different type of contraception since VIRACEPT may reduce the effectiveness of oral contraceptives.

[subhead]
Special considerations
Before you take Viagra® (sildenafil) with VIRACEPT, talk to your doctor about possible drug interactions and side effects. If you take Viagra and VIRACEPT together, you may be at increased risk of side effects of Viagra such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If an erection lasts longer than 4 hours, you should seek immediate medical assistance to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

It is not recommended to take VIRACEPT with the cholesterol-lowering drugs Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible drug interactions. There is also an increased risk of drug intercations between VIRACEPT and Lipitor® (atorvastatin) and Baycol® (cerivastatin); talk to your doctor before you take either of these cholesterol reducing drugs with VIRACEPT.

Taking St. John's wort (hypericum perforatum), an herbal product sold as a dietary supplement, or products containing St. John's wort with VIRACEPT is not recommended. Talk with your doctor if you are taking or are planning to take St. John's wort. Taking St. John's wort may decrease VIRACEPT levels and lead to increased viral load and possible resistance to VIRACEPT or cross resistance to other antiretroviral drugs.

[section heading]
How should VIRACEPT be taken with other anti-HIV drugs?

Taking VIRACEPT together with other anti-HIV drugs increases their ability to fight the virus. It also reduces the opportunity for resistant viruses to grow. Based on your history of taking other anti-HIV medicine, your doctor will direct you on how to take VIRACEPT and other anti-HIV medicines. These drugs should be taken in a certain order or at specific times. This will depend on how many times a day each medicine should be taken. It will also depend on whether it should be taken with or without food.

Nucleoside analogues: No drug interaction problems were seen when VIRACEPT was given with:
Retrovir (zidovudine, AZT)
Epivir (lamivudine, 3TC)
Zerit (stavudine, d4T)

Videx® (didanosine, ddI)

If you are taking both Videx (ddI) and VIRACEPT:
Videx should be taken without food, on an empty stomach. Therefore, you should take VIRACEPT with food one hour after or more than two hours before you take Videx.

Nonnucleoside reverse transcriptase inhibitors (NNRTIs):
When VIRACEPT is taken together with:
Viramune® (nevirapine)
The amount of VIRACEPT in your blood is unchanged. A dose adjustment is not needed when VIRACEPT is used with Viramune.
Sustiva™ (efavirenz)
The amount of VIRACEPT in your blood may be increased. A dose adjustment is not needed when VIRACEPT is used with Sustiva.
Other NNRTIs
VIRACEPT has not been studied with other NNRTIs.

Other protease inhibitors:
When VIRACEPT is taken together with:
Crixivan® (indinavir)
The amount of both drugs in your blood may be increased. Currently, there are no safety and efficacy data available from the use of this combination.
Norvir™ (ritonavir)
The amount of VIRACEPT in your blood may be increased. Currently, there are no safety and efficacy data available from the use of this combination.
Invirase® (saquinavir)
The amount of saquinavir in your blood may be increased. Currently, there are no safety and efficacy data available from the use of this combination.

[section heading]
What are the side effects of VIRACEPT?

Like all medicines, VIRACEPT can cause side effects. Most of the side effects experienced with VIRACEPT have been mild to moderate. Diarrhea is the most common side effect in people taking VIRACEPT, and most adult patients had at least mild diarrhea at some point during treatment. In clinical studies, about 15-20% of patients receiving VIRACEPT 750 mg (three tablets) three times daily or 1250 mg (five tablets) two times daily had four or more loose stools a day. In most cases, diarrhea can be controlled using antidiarrheal medicines, such as Imodium® A-D (loperamide) and others, which are available without a prescription.

Other side effects that occurred in 2% or more of patients receiving VIRACEPT include nausea, gas, and rash.

There were other side effects noted in clinical studies that occurred in less than 2% of patients receiving VIRACEPT. However, these side effects may have been due to other drugs that patients were taking or to the illness itself. Except for diarrhea, there were not many differences in side effects in patients who took VIRACEPT along with other drugs compared with those who took only the other drugs. For a complete list of side effects, ask your doctor, nurse, or pharmacist.

[section heading]
How should I take VIRACEPT?

VIRACEPT is available only with your doctor's prescription. Your doctor may prescribe the light blue VIRACEPT Tablets either as 1250 mg (five tablets) taken two times a day or as 750 mg (three tablets) taken three times a day. VIRACEPT should always be taken with a meal or a light snack. VIRACEPT tablets are film-coated to help make the

tablets easier to swallow.

Take VIRACEPT exactly as directed by your doctor. Do not increase or decrease any dose or the number of doses per day. Also, take this medicine for the exact period of time that your doctor has instructed. **Do not stop taking VIRACEPT without first consulting with your doctor, even if you are feeling better**.

Only take medicine that has been prescribed specifically for you. Do not give VIRACEPT to others or take medicine prescribed for someone else.

The dosing of VIRACEPT may be different for you than for other patients. **Follow the directions from your doctor, exactly as written on the label.** The amount of VIRACEPT in the blood should remain somewhat consistent over time. Missing doses will cause the concentration of VIRACEPT to decrease; therefore, **you should not miss any doses.** However, if you miss a dose, you should take the dose as soon as possible and then take your next scheduled dose and future doses as originally scheduled.

[subhead]
Dosing in adults (including children 14 years of age and older)

The recommended adult dose of VIRACEPT is 1250 mg (five tablets) taken two times a day or 750 mg (three tablets) taken three times a day. Each dose should be taken with a meal or light snack.

[subhead]
Dosing in children 2 to 13 years of age

The VIRACEPT dose in children depends on their weight. The recommended dose is 20 to 30 mg/kg (or 9 to 14 mg/pound) per dose,

taken three times daily with a meal or light snack. This can be administered either in tablet form or, in children unable to take tablets, as VIRACEPT Oral Powder.

Dose instructions will be provided by the child's doctor. The dose will be given three times daily using the measuring scoop provided, a measuring teaspoon, or one or more tablets depending on the weight and age of the child. The amount of oral powder or tablets to be given to a child is described in the chart below.

[chart]

Pediatric Dose to Be Administered Three Times Daily				
Body Weight Kg	 Lb	Number of Level Scoops*	Number of Level Teaspoons†	Number of Tablets
7 to <8.5	15.5 to <18.5	4	1	--
8.5 to <10.5	18.5 to <23	5	1 ¼	--
10.5 to <12	23 to <26.5	6	1 ½	--
12 to <14	26.5 to <31	7	1 ¾	--
14 to <16	31 to <35	8	2	--
16 to <18	35 to <39.5	9	2 ¼	--
18 to <23	39.5 to <50.5	10	2 ½	2
≥23	≥50.5	15	3 ¾	3

In measuring oral powder, the scoop or teaspoon should be level.

* 1 level scoop contains 50 mg of VIRACEPT. Use only the scoop provided with your VIRACEPT bottle.

† 1 level teaspoon contains 200 mg of VIRACEPT. Note: **A measuring teaspoon used for dispensing medication** should be used for measuring

VIRACEPT Oral Powder. Ask your pharmacist to make sure you have a medication dispensing teaspoon.

[subhead]
How should VIRACEPT Oral Powder be prepared?

The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk, dietary supplements, or dairy foods such as pudding or ice cream. Once mixed, the entire amount must be taken to obtain the full dose.

Do **not** mix the powder with any acidic food or juice, such as orange or grapefruit juice, apple juice, or apple sauce, because this may create a bitter taste.

Once the powder is mixed, if it is not consumed immediately, it must be stored under refrigeration for up to 6 hours. Do **not** heat the mixed dose once it has been prepared.

Do **not** add water to bottles of oral powder.

VIRACEPT powder is supplied with a scoop for measuring. For help in determining the exact dose of powder for your child, please ask your doctor, nurse, or pharmacist.

VIRACEPT Oral Powder contains aspartame, a low-calorie sweetener, and therefore should not be taken by children with phenylketonuria (PKU).
[section heading]
How should VIRACEPT be stored?

Keep VIRACEPT and all other medicines out of the reach of children. Keep bottle closed and store at room temperature (between 59°F and 86°F) away from sources of moisture such as a sink or other damp

place. Heat and moisture may reduce the effectiveness of VIRACEPT.

Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

Discuss all questions about your health with your doctor. If you have questions about VIRACEPT or any other medication you are taking, ask your doctor, nurse, or pharmacist. You can also call 1.888.VIRACEPT (1.888.847.2237) toll free.

**

Issued xxx

Call 1.888.VIRACEPT

[icon/logo] **Agouron**®
Pharmaceuticals Inc.

La Jolla, California, 92037, USA

**Trademark paragraph deleted.